REMARKS

1. Status of the claims

The Office Action Summary indicates that claims 8-11, 21, and 30-35 are pending and that claims 8-11 and 30-32 stand withdrawn from consideration as being drawn to non-elected subject matter. Claims 33-35 stand rejected.

Applicants note for the record that no mention is made as to the status of claim 21. Applicants respectfully request clarification for the record as to the status of claim 21. Applicants note that claim 21 was a member of Group I. Applicants elected the claims of Group III (*i.e.*, claims 33-35). Presumably, claim 21 stands withdrawn. Applicants have indicated it as "Withdrawn" in the "Listing of the Claims."

Applicants have amended claims 33 and 34. Support for the subject claim amendments can be found at least in the original claims and in the examples.

2. Acknowledgement of Information Disclosure Statements

Applicants appreciate the acknowledgement of the Information Disclosure Statements filed September 6, 2005 and October 4, 2005.

3. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 33-34 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims stand rejected for lack of antecedent basis for the phrase "the natriuretic peptide."

Applicants have amended claim 33 such that it no longer recites "substance," thereby mooting the rejection as to "the natriuretic peptide". Accordingly, Applicants respectfully request withdrawal of the rejection, and allowance of claims 33-34.

4. Claim Objections

Claim 34 is objected to because the claim uses the term "arterial" natriuretic peptide. Applicants have amended claim 34 to correctly recite "atrial". Accordingly, Applicants

respectfully request withdrawal of the objection and allowance of claim 34.

5. Claim Rejections Under 35 U.S.C. § 103

5.1 Claims 33 and 34

Claims 33 and 34 stand rejected under 35 U.S.C. § 103(a) as obvious over (1) Blaine (U.S. Patent No. 4,652,549) ["Blaine"] as evidenced by (2) L. Cao et al., *Hypertension* 25(2): 227-234 (1995) ["Cao"] or (3) E. Espiner, *Curr. Opin. In Endocrinology and Diabetes* 5: 205-210 (1998) ["Espiner"], and further in view of (4) Tilley et al., *Recent Advances in Studies on Cardiac Structure and Metabolism* 10: 641-53 (1975) [Abstract only] ["Tilley"].

Applicants traverse the rejection. Applicants disagree with the Office's analysis and conclusion. First, in order to make a *prima facie* case of obviousness, according to M.P.E.P. § 2142, the references must provide some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *See,* M.P.E.P. § 2142 cited to *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *see also,* M.P.E.P. § 2143. Additionally, "under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co.,* 148 U.S.P.Q. 459, 466-467 (1966).

Blaine. Blaine is asserted for allegedly teaching a "method of treatment of cardiac hypertrophy using atrial natriuretic peptide (ANP) and fragments thereof. *See* abstract, summary, col. 3, lines 11-20, and claims 1-8. In particular, the treatment reverses cardiac hypertrophy and reduces heart weight – see Example 11, col. 4, lines 23-41. Thus, the

reference teaches method of reducing heart weight after cardiac hypertrophy. With regard to the term 'a substance that acts on guanylyl cyclase A natriuretic receptor and accelerates production of cyclic guanosine monophosphate', as discussed in the course of preceding prosecution, natriuretic peptide acts on guanylyl cyclase A natriuretic receptor and thus accelerates production of cyclic guanosine monophosphate. It is well known that ANP, as well as its analogs stimulate guanylate cyclase A and production of cGMP." Office Action, page 3.

The Office admits that Blaine fails to suggest "that cardiac hypertrophy has to be a result of chronic cardiac hypertrophy which cardiac hypertrophy produces pulmonary congestion." Office Action, page 4. However, the Office asserts that it would have been obvious to one skilled in the art that the method of Blaine generally addressing cardiac hypertrophy would have been applicable to "chronic hypertrophy which produces pulmonary congestion". Applicants disagree with this conclusion.

As previously asserted, Blaine does not teach or suggest treatment of a cardiac dysfunction that produces pulmonary congestion. As amended, claims 33-34 are directed to the decrease of ventricle weight, which has once been increased by the cardiac hypertrophy by the administration of a natriuretic peptide. Blaine is directed to the decrease of the water content of the heart only, as discussed in col. 4, line 28 of Blaine ("grams H_2O per 100 grams tissue"). The phenomenon of the increase or decrease of the water content in a heart is distinguishable from the increase or decrease of ventricle weight. Blaine does not suggest nor teach that administering a natriuretic peptide will decrease the weight of a ventricle, which has once been increased by cardiac hypertrophy. Applicants discuss in the specification at least in Table 1 on page 12; page 13, lines 9-10; Table 2 on page 15; page 16, lines 7-11; page 19, lines 9-11; and Figure 2 that the decrease of the ventricle weight and the decrease of the ventricle weight/body weight.

Additionally, Applicants note that the ratio of the ventricle weight/body weight has been recognized in the art as a measure of cardiac hypertrophy. Applicants submit herewith an exemplary article that discusses these ratios in paragraph 2 on page 253 such ratios (G. Bruckschlegel et al., *Hypertension* 25: 250-259, 1995).

Blaine does not discuss or suggest pulmonary congestion whatsoever. Additionally, Blaine does not teach or suggest a method of decreasing heart weight or a method of recession of cardiac hypertrophy after the cardiac hypertrophy has been established.

Additionally, Blaine does not teach or suggest that a compound that will act on guanylyl cyclase A (GC-A) natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate will also reduce pulmonary congestion. As there is no suggestion, let along a teaching in this regard, there can be no expectation that the result may occur. There must be evidence to show that the result must occur, and not a mere possibility in the realm of possibilities. *See, e.g., In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Applicants also point out that prior to the priority date of the current application, *in vivo* effects of ANP on cardiomyocytes had not been known. Therefore, it was not known that ANP inhibited or could have inhibited the growth of the cardiomyocytes or protein synthesis in the cardiomyocytes. In fact, the opposite had been known in the art at the time. The enclosed article of M. Koide et al., (*Differentiation*, 61: 1-22, 1996) reported that ANP in fact promoted the growth of chick embryonic cardiomyocytes. *See*, Koide et al., at Abstract and page 1.

Cao. Cao is asserted by the Office for purportedly demonstrating "that the hypertrophy-reducing effect of the natriuretic peptides is due to their interaction with guanylyl cyclase A natriuretic peptide receptor and is further mediated by formation of cGMP (p. 231, and p. 233, second paragraph." Office Action, page 3.

A reference must be assessed for what it teaches *as a whole*. *See e.g.,* M.P.E.P. § 2141.02. Cao indicates on page 233 that "the possibility of a role of the natriuretic peptide receptors in controlling fibroblast growth in the cardiac interstitium is intriguing." By no means were the authors' findings demonstrate that fibroblast growth could be controlled. Additionally, the assertion that the natriuretic peptides were capable of reducing agonist-stimulated [^{3}H]-thymidine incorporation in cell cultures is not the same as proving that the peptides can be used as a method of treatment for cardiac hypertrophy, let alone a specific type of cardiac hypertrophy. Cao even states that "these are cultured cells and may not reflect the in vivo receptor phenotype with fidelity." Cao, at best, presents an obvious to try argument. But, "obvious to try" is not the proper test with which to prove obviousness. *In*

re O'Farrell, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988). There is no teaching or blaze mark linking the relevant parameters of each of the references to achieve the claimed method.

Applicants also assert that the Office's presentation of what Cao teaches is inaccurate, given the above quotes and its teachings as whole. *See,* the "Discussion" portion of Cao on pages 232-233. Cao fails to teach or suggest anything with regard to the use of the natriuretic peptides for a method of treating a cardiomyopathy involving hypertrophy, let alone provide an expectation that such a method would be successful.

Cao is being asserted by the Office in attempt to cure the defects of Blaine. However, we note that Blaine was published March 24, 1987 and is based on an application that was filed January 22, 1985. The Cao reference published in 1995. Yet, ten years after the initial filing of Blaine, Cao continues to indicate that there is only a possible role for natriuretic peptide receptors in controlling fibroblast growth. Cao, at p. 233, left col. The long felt need to treat the disorder remained, yet no one until Applicants claimed this method of treatment. Therefore, Cao fails to teach or suggest the claimed invention alone, and also fails to cure the defects of Blaine.

Espiner. Espiner is asserted for allegedly "teaching that natriuretic peptides is due to their interaction with guanylyl cyclase A natriuretic peptide receptor and further mediated by formation of cGMP (p. 205, last paragraph)." Pages 3-4, Office Action. First, Espiner was published after the date to which the instant case claims benefit. The Office asserts that while the reference has a publication date later than the priority date of the instant application, the reference is a review that describes studies preceding the instant application. Additionally, the reference is merely being used to demonstrate well known mechanisms of action. *See,* Office Action, fn. 1, page 4.

Applicants submit that the asserted portion of Espiner cannot be relied upon. This section does not refer to any reference, let alone a reference published prior to the February 1997 date to which this application claims benefit. Accordingly, the Office improperly relies upon the Espiner reference in support of its allegation that claims 33-34 are obvious. The reference accordingly should be dropped from the Office's rejection.

Tilley. The Office apparently asserts Tilley for teaching that heart failure manifests itself in pulmonary congestion. Office Action, page 4. Tilley is in fact directed to dilated

cardiomyopathy in dogs. The cardiac myopathy was evidenced by severe enlargement of all cardiac chambers and evidence of congestive heart failure. *See,* Abstract, Tilley. At necropsy, dilation was observed of the atrioventricular annular rings and massive atrial dilation was also observed. *Id.* Dilated cardiomyopathy does not lead to increased heart weight after cardiac hypertrophy. Instead, the heart walls become thin, and not thick. Claims 33-34 as amended are directed toward "a method for decreasing ventricle weight which has once increased by the cardiac hypertrophy...." Tilley is not directed to the subject matter of the claims, and therefore does not teach the subject matter of the claimed invention. Additionally, there would be no suggestion to combine the reference with Blaine or the other references, as Tilley is directed to a different cardiomyopathy.

For at least the reasons asserted above, the rejection of claims 33 and 34 should be withdrawn as no *prima facie* case of obviousness has been adduced. Applicants respectfully request allowance of the claims.

5.2 Claim 35

Claim 35 stands rejected under 35 U.S.C. § 103(a) as being allegedly "unpatentable over claims 33, 34 are rejected under 35 U.S.C. 103(a) as obvious over Blaine as evidenced by Cao et al. or Espiner and further in view of Tilley et al. as applied to claims 33,34 above, and further in view of Salito et al (Circullation, 76:, 115-124, 1987)." Office Action, pages 4-5. The Office asserts that with regard to claim 35, "BNP is functional equivalent of ANP – see Salito reference, for example, as discussed in applicant's response of 0906/2005, p. 6).

Applicants traverse the rejection. First, no *prima facie* case of obviousness has been adduced by the Office as asserted by the combination of the Blaine, Cao, Espiner, and Tilley references as discussed *supra.* Applicants note that the "Salito" reference is in fact Saito et al., *Circulation* 76: 115-124, 1987). Applicants assert that Saito does not cure the defects of the four other references in any combination for at least the following reasons.

The Office makes a statement that BNP is a functional equivalent of ANP without explaining how this would render the claim obvious over the set of five references. Therefore, there is no *prima facie* case, because no analysis of *why* the statement renders the claim obvious in view of the other references is asserted by the Office. Applicants are under

no obligation to respond pursuant to M.P.E.P. § 2142, given that the analysis as required under § 2142 has not been performed. Additionally, Saito fails to cure the defects inherent to Blaine, Cao, Espiner, and Tilley. Accordingly, no *prima facie* case of obviousness as to claim 35 has been adduced. Applicants respectfully request withdrawal of the rejection allowance of the claim.

CONCLUSION

In view of the foregoing, Applicants respectfully request the entry of the amendments to place the application in condition for allowance, or in the alternative, in better form for appeal.

If there are any other fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the attached papers, such an extension is requested and the fee should also be charged to our Deposit Account.

If any matters remain outstanding, the Examiner is invited to contact the undersigned representative regarding this matter.

Respectfully submitted,
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